(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2001 (23.08.2001)

PCT

(10) International Publication Number
WO 01/60409 A1

(51) International Patent Classification[7]: A61K 47/02, 47/18, 47/26, 47/34, 47/10

(21) International Application Number: PCT/EP01/01155

(22) International Filing Date: 5 February 2001 (05.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/504,741 16 February 2000 (16.02.2000) US

(71) Applicant *(for all designated States except US)*: **MERIAL LIMITED** [GB/GB]; 27 Knightsbridge, London SW1 (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **JUN, Chen** [CN/US]; 1 Meyer Court, Robbinsville, NJ 08691 (US).

(74) Agents: **JACOBSON, Claude** et al.; Cabinet Lavoix, 2, place d'Estienne d'Orves, F-75441 Paris Cedex 09 (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/60409 A1

(54) Title: IMPROVED PASTE FORMULATIONS

(57) Abstract: This invention provides for a pharmaceutical or veterinary paste formulation comprising: an effective amount of a therapeutic agent; fumed silica; a viscosity modifier; a hydrophilic carrier; optionally, an absorbent; and optionally, a colorant, stabilizer, surfactant, or preservative. This invention also provides for methods of using these formulations for treating various disease states as well.

TITLE OF THE INVENTION

IMPROVED PASTE FORMULATIONS

FIELD OF THE INVENTION

This invention provides for improved paste formulations suitable for pharmaceutical and veterinary use as well as methods for treating various disease states using these formulations. This invention also provides for an improved method for manufacturing paste formulations.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts the change of viscosity as a function of increased CAB-O-SIL content wherein no viscosity modifier was added.

Fig. 2 depicts the impact of the viscosity modifier, PEG 300, on the paste viscosity of initial and after storage for 6 days at 60°C.

Fig. 3 depicts the schematic representation of the competition of excess PEG molecules with the crosslinking PEG molecules.

Fig. 4 depicts the sheer sensitivity study of the intermediate product at low sheer.

Fig. 5 depicts the sheer sensitivity study of the end product at high sheer.

Fig. 6 depicts the powder X-ray diffraction (XRPD) pattern of form A.

Fig. 7 depicts the XRPD pattern of form B.

BACKGROUND OF THE INVENTION

Therapeutic agents are administered to animals and humans by a variety of routes. These routes include, for example, oral ingestion, topical application or parental administration. The particular route selected by the practitioner depends upon factors such as the physiochemical properties of the therapeutic agent, the condition of the host, and economics.

One method of formulating a therapeutic agent for oral, topical, dermal or subdermal administration is to formulate the therapeutic agent as a paste. Pastes have the advantage of being relatively easy to use. The disadvantage associated with their use is that often these products typically do not retain good chemical and physical stability over the shelf-life of the product. Hence, there is a need for improved paste formulations which do not exhibit the these undesirable properties.

One of the causes of these disadvantages is the inclusion of fumed silica as a viscosity agent. Fumed silica is commercially available and sold, for example, under the trade names of CAB-O-SIL (Cabot, TD11) and AEROSIL (Degussa, Technical Bulletin Pigments, No. 11 and No. 49). Fumed silica is an extremely light material (density 0.04 g/ml), which makes its handling and processing difficult. Moreover, because of its light density, fumed silica, when mixed with a vehicle, introduces a significant amount of air into the product. This occurs even at the relatively small amounts (6 to 8%) typically used to make pastes (6 to 8%). Unless the paste is processed under vacuum or a deareation step is added at the end of the process, it is not possible to remove such large amounts of air bubbles from the paste.

In order to demonstrate the problems associated with using fumed silica such as CAB-O-SIL, the viscosity of a paste as a function of CAB-O-SIL content was measured. Fig. 1 depicts the change of viscosity of the paste where no viscosity modifier was added. Triacetin

was used as the vehicle in this study. When the CAB-O-SIT content was less than 5%, the paste remained thin as a free flow liquid and entrapped air could easily escape. After 5%, the viscosity increased dramatically and the additional air brought into the paste by the CAB-O-SIL could not escape and stayed in the paste. When about 7% of CAB-O-SIL was added, the paste had a penetration value of 35 mm. This amount is comparable with the initial penetration value of other commercially known pastes such as GASTROGARD (20-40 mm). Hence, in the absence of a viscosity modifier, at least 7% of CAB-O-SIL was needed to make pastes with useful viscosity. Because of the low density of CAB-O-SIL (0.04 g/ml), the amount of entrapped air is significant. Thus, unless processing under vacuum or adding a deareation step at the end, it is impossible to remove such large amounts of air in the paste and cannot control the accuracy of the dose.

Viscosity modifiers include compounds that have two or more functional groups which are capable of forming hydrogen bonds with the silanols on the surface of the fumed silica particles. Compounds which function as viscosity modifier include, for example, the polyethylene glycols ("PEGs"). These compounds are liquid and solid polymers which correspond to the general formula $H(OCH_2CH_2)_nOH$, where n is greater than or equal to 4, and are described in "The Merck Index", 10th ed., M. Windholz and S. Budavari eds., p. 1092, Merck & Co., Inc., Rahway, NJ (1983).

While not wishing to be bound by theory, in order to understand the mechanism of the viscosity modifiers, it is necessary to understand how CAB-O-SIL thickens a formulation. The hydrogen bonds between the silanol groups on the surface of the CAB-O-SIL particles are responsible for its thickening effect. CAB-O-SIL particles are connected through these hydrogen bonds to form a three-dimension network. The viscosity modifiers have two or more functional

groups (e.g., -OH or -NH_2). These groups form hydrogen bonds with the silanols on the surface of CAB-O-SIL particles. These viscosity modifiers act as crosslinkers to extend the network structure and also increase the crosslinking density. This is why the addition of a small amount of the viscosity modifiers dramatically increased the viscosity of the pastes.

In order to demonstrate this, placebo pastes containing 4% CAB-O-SIL and 0.1-3.0% polyethylene glycol ("PEG") 300 in triacetin were prepared and their viscosity values were measured using penetrometer (Fig. 2). Before the addition of PEG 300, the viscosity was too low to be tested on penetrometer (>65 mm). The viscosity jumped dramatically with just the addition of only 0.1% PEG 300. The viscosity increased further when more PEG 300 was added. After the PEG level reached 0.5%, the viscosity increase plateaued. From 0.5-3.0%, the viscosity remained about the same, although a slight decrease in viscosity was seen when more than 2% PEG was added.

Fig. 3 depicts what is believed to be happening at the molecular level. Fig. 3 depicts the competition of excess PEG molecules with the crosslinking PEG molecules at the molecular level. The figure indicates that the silanol groups on the surface of CAB-O-SIL particles were saturated when more than 0.5% PEG was added. The extra PEG molecules could no longer increase the viscosity because it could not find two free silanol groups on two different particles to increase further the viscosity. On the contrary, the free PEG molecules actually compete with the bonded PEG molecules that crosslinks two particles (Fig. 3). As a result, some of the crosslinks dissociate and the viscosity decreases slightly. Based on Fig. 2, the ideal range of PEG 300 is about 0.2% to about 1.5% for this particular paste.

Thus, as depicted in Fig. 1, the prior pastes use a relatively high amount of fumed silica to achieve the proper viscosity. The effect of this is that a large amount of air will be

entrapped into the paste, which causes, for example, dose inaccuracy, shrinkage, liquid separation (whipping) and discoloration of the paste. Further, the therapeutic agent may also oxidize. Moreover, when a large amount of fumed silica is used in an oral paste, the paste imparts a sandy feel to the mouth. This sandy feel causes the product less palatable. Furthermore, the manufacturing costs to prepare the pastes are expensive because the process must occur under vacuum or a subsequent deareation step at the end of the process is required. Additional manufacturing costs are incurred because fumed silica is relatively expensive and very difficult to handle due to its extremely low density. The present invention overcomes these as well as other disadvantages.

SUMMARY OF THE INVENTION

The present invention provides for a stable paste formulation for a wide range of veterinary and pharmaceutical products. The present invention also provides for an improved process to make the inventive paste products. The formulations of the present invention exhibit good chemical and physical stability over the shelf life and maintain the chemical integrity, texture, consistency and viscosity over a wide temperature range. The inventive manufacturing process provides for a simple, fast and economical process for preparing the inventive paste formulations that avoids heating and cooling during manufacturing and entrapment of air, a common problem in the manufacturing of paste dosage forms.

These and other embodiments are disclosed or are obvious, from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

The present invention provides for a pharmaceutical or veterinary paste formulation comprising:

(a) an effective amount of a therapeutic agent;

(b) fumed silica;

(c) a viscosity modifier;

(d) a carrier;

(e) optionally, an absorbent; and

(f) optionally, a colorant, stabilizer, surfactant, or preservative.

This invention also provides for a process for preparing a paste formulation comprising the steps of:

(a) dissolving or dispersing the therapeutic agent into the carrier by mixing;

(b) adding the fumed silica to the carrier containing the dissolved therapeutic agent and mixing until the silica is dispersed in the carrier;

(c) allowing the intermediate formed in (b) to settle for a time sufficient in order to allow the air entrapped during step (b) to escape; and

(d) adding the viscosity modifier to the intermediate with mixing to produce a uniform paste.

The steps are illustrating, but not limiting. For Example, step (a) can be moved to the last step.

More preferred are pharmaceutical and veterinary pastes comprising:

(a) a therapeutic agent selected from the group consisting of insecticides, acaricides, parasiticides, growth enhancers, oil-soluble NSAIDS or a proton pump inhibitor;

(b) fumed silica;

(c) a viscosity modifier;

(d) an absorbent;

(e) a colorant; and

(f) a carrier which is triacetin, a monoglyceride, a diglyceride, or a triglyceride.

Also preferred are pastes comprising:

(a) a therapeutic agent selected from the group consisting of avermectins, milbemycins, nordulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridyl methyl derivatives, phenylpyrazoles, COX-2 inhibitors or 2-(2-benzimidazolyl)-pyrimidine derivatives;

(b) fumed silica;

(c) a viscosity modifier;

(d) an absorbent;

(e) a colorant; and

(f) a hydrophilic carrier which is triacetin, a monoglyceride, a diglyceride, or a triglyceride.

The above compositions wherein the viscosity modifier is PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxyethylene (20) sorbitan mono-oleate (polysorbate 80 or Tween 80), polyoxamers (e.g.,

Pluronic L 81); the absorbent is magnesium carbonate, calcium carbonate, starch, or cellulose and its derivatives; and the colorant is titanium dioxide iron oxide, or FD&C Blue #1 Aluminum Lake are most especially preferred.

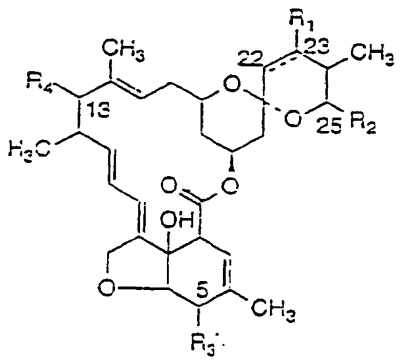
The therapeutic agents which are used in the inventive formulations are those which are known to the practitioner as agents which may be formulated as pastes. Classes of therapeutic agents contemplated by the inventive formulations include insecticides, acaricides, parasiticides, growth enhancers, oil-soluble, nonsteroidal anti-inflammatory drugs (NSAIDS), proton pump inhibitors and antibacterial compounds. Specific classes of compounds which fall within these classes include, for example, avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridylmethyl derivatives, phenylpyrazoles, COX-2 inhibitors, 2-(2-benzimidazolyl)-pyrimidines derivatives and macrolide antibiotics.

The avermectin and milbemycin series of compounds are potent anthelmintic and antiparasitic agents against a wide range of internal and external parasites. The compounds which belong to this series are either natural products or are semi-synthetic derivatives thereof. The structure of these two series of compounds are closely related and they both share a complex 16-membered macrocyclic lactone ring; however, the milbemycin do not contain the aglycone substituent in the 13-position of the lactone ring. The natural product avermectins are disclosed in U.S. Patent 4,310,519 to Albers-Schonberg, *et al.*, and the 22, 23-dihydro avermectin compounds are disclosed in Chabala, *et al.*, U.S. Patent 4,199,569. For a general discussion of avermectins, which include a discussion of their uses in humans and animals, see "Ivermectin and Abamectin," W.C. Campbell, ed., Springer-Verlag, New York (1989). Naturally occurring milbemycins are described in Aoki *et al.*, U.S. Patent 3,950,360 as well as in the various

references cited in "The Merck Index" 12th ed., S. Budavari, Ed., Merck & Co., Inc. Whitehouse Station, New Jersey (1996). Semisynthetic derivatives of these classes of compounds are well known in the art and are described, for example, in U.S. Patent 5,077,308, U.S. Patent 4,859,657, U.S. Patent 4,963,582, U.S. Patent 4,855,317, U.S. Patent 4,871,719, U.S. Patent 4,874,749, U.S. Patent 4,427,663, U.S. Patent 4,310,519, U.S. Patent 4,199,569, U.S. Patent 5,055,596, U.S. Patent 4,973,711, U.S. Patent 4,978,677, and U.S. Patent 4,920,148.

Avermectins and milbemycins share the same common 16-membered macrocyclic lactone ring; however, milbemycins do not possess the disaccharide substituent on the 13-position of the lactone ring.

While many avermectin compounds are known in the art, a representative structure of the class of compounds is as follows:



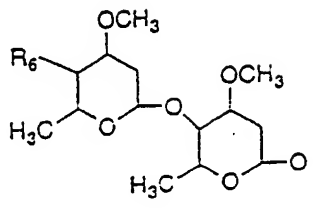
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;

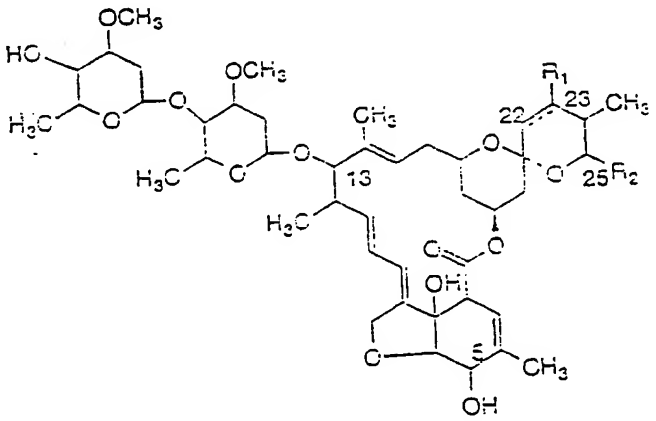
R_3 is hydroxy, methoxy or = NOR_5 where R_5 is hydrogen or lower alkyl; and

R_4 is hydrogen, hydroxy or



where R_6 is hydroxy, amino, mono-or di-lower alkylamino or lower alkanoylamino.

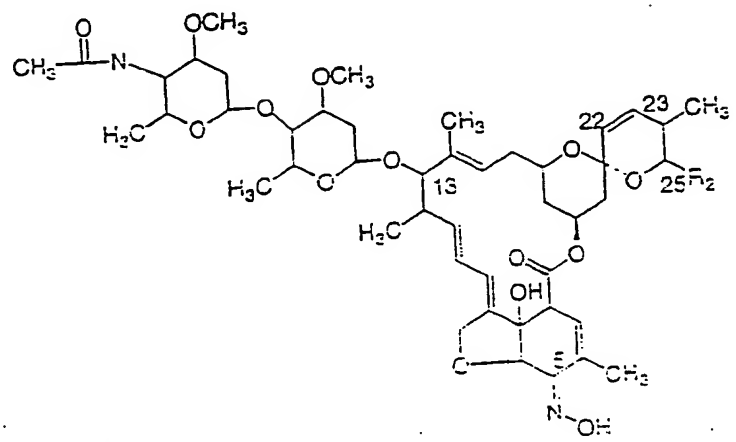
The preferred compounds are avermectin Bla/Blb (abamectin), 22,23-dihydro avermectin Bla/Blb (ivermectin) and the 4"-acetylamino-5-ketoximino derivative of avermectin Bla/Blb. Both abamectin and ivermectin are approved as broad spectrum antiparasitic agents. The structures of abamectin and ivermectin are as follows:



wherein for abamectin the broken line represents a double bond and R_1 is not present and for ivermectin the double bond represents a single bond and R_1 is hydrogen; and

R_2 is isopropyl or sec-butyl.

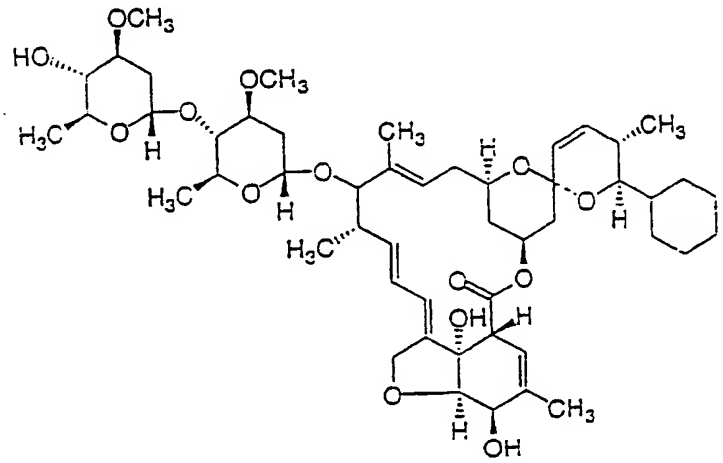
The 4"-acetyl amino-5-ketoximino derivatives of avermectin Bla/Blb has the following structural formula:



where R_2 is isopropyl or sec-butyl.

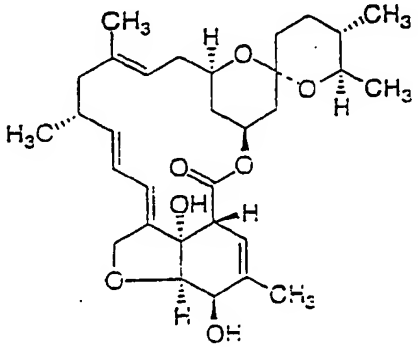
The avermectin products are generally prepared as a mixture of at least 80% of the compound where R_2 is sec-butyl and no more than 20% of the compound where R_2 is isopropyl.

Other preferred avermectins, include ememectin, epinomectin and doramectin. Doramectin is disclosed in U.S. Patent 5,089,490 and EP 214 738. This compound has the following structure:

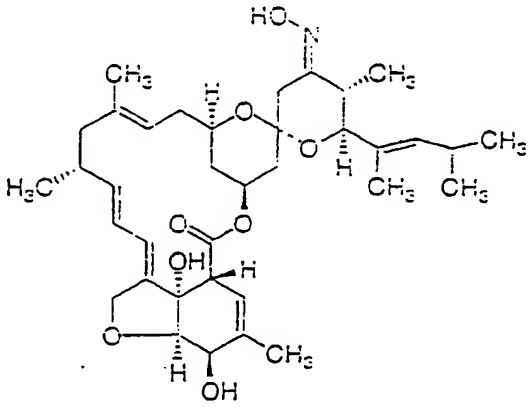


In the present formulations, ivermectin is especially preferred.

A representative structure for a milbemycin is that for milbemycin α_1:



An especially preferred milbemycin is moxidectin, whose structure is as follows:



The compound is disclosed in U.S. Patent No. 5,089,490.

The monosaccharide avermectin derivatives are also preferred especially where an oxime substitution is present on the 5-position of the lactone ring. Such compounds are described, for example, in EP 667,054. Selamectin is an especially preferred compound of this class of derivatives.

Nodulisporic acid and its derivatives are a class of acaricidal, antiparasitic, insecticidal and anthelmintic agents well known to a practitioner of the art. These compounds are used to treat or prevent infections in humans and animals. These compounds are described,

for example, in U.S. Patent 5,399,582 and WO 96/29073. Additionally, the compounds can be administered in combination with other insecticides, parasiticides, and acaricides. Such combinations include anthelmintic agents, such as those discussed above which include ivermectin, avermectin, and emamectin, as well as other agents such as thiabendazole, febantel or morantel; phenylpyrazoles such as fipronil; and insect growth regulators such as lufenuron. Such combinations are also contemplated in the present invention.

Generally, all classes of insecticides are provided for in this invention. One example of this class include substituted pyridylmethyl derivatives such as imidacloprid. Agents of this class are described, for example, in U.S. Patent 4,742,060 or in EP 892,060. It would be well within the skill level of the practitioner to decide which individual compound can be used in the inventive formulation to treat a particular infection of an insect.

Phenylpyrazoles are another class of insecticides which possess excellent insecticidal activity against all insect pests including blood-sucking pests such as ticks, fleas etc., which are parasites on animals. This class of agents kills insects by acting on the gamma-butyric acid receptor of invertebrates. Such agents are described, for example, in U.S. Patent No. 5,567,429, U.S. Patent No. 5,122,530, and EP 295,117. An especially preferred phenylpyrazole is fipronil, whose chemical name is 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylpyrazole. Fipronil is well known in the art as a flea and tick agent. It would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulations.

Insect growth regulators are another class of insecticides or acaricides, which are also provided for in the inventive formulations. Compounds belonging to this group are well known to the practitioner and represent a wide range of different chemical classes. These

compounds all act by interfering with the development or growth of the insect pests. Insect growth regulators are described, for example, in U.S. Patent 3,748,356; U.S. Patent 3,818,047; U.S. Patent 4,225,598; U.S. Patent 4,798,837; and U.S. Patent 4,751,225, as well as in EP 179,022 or U.K. 2,140,010. Especially preferred insect growth regulators include diflubenzuron, lufenuron, methoprene, phenoxycarb, pyriproxyfen, and cyromazine. Again, it would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulation.

Estrogens, progestins, and androgens refers to classes of chemical compounds which are also well known to a practitioner in this art and used, for example, to regulate fertility in humans and animals. In fact, estrogens and progestins are among the most widely prescribed drugs and are used, for example, alone or in combination for contraception or hormone replacement therapy in post menopausal women. Estrogens and progestins occur naturally or are prepared synthetically. This class of compounds also includes estrogens or progesterone receptor antagonists. Antiestrogens, such as tamoxifen and clomiphene, are used to treat breast cancer and infertility. Antiprogestives are used as contraceptives and anticancer drugs, as well as to induce labor or terminate a pregnancy.

The androgens and antiandrogens structurally related to the estrogens and progestins as they are also biosynthesized from cholesterol. These compounds are based on testosterone. Androgens are used for hypogonadism and promote muscle development. Antiandrogens are used, for example, in the management of hyperplasia and carcinoma of the prostate, acne, and male pattern baldness as well as in the inhibition of the sex drive in men who are sex offenders. Estrogen, progestins, and androgens are described, for example, in "Goodman & Gilman's The Pharmacological Basis of Therapeutics," 9th ed., J.G. Handman and L. Elimbird,

eds., Ch. 57 to 60, pp. 1411- 485, McGraw Hill, New York (1996) or in "Principles of Medicinal Chemistry," 2nd ed., W.O. Foye, ed., Ch. 21, pp. 495-559, Lea & Febiger, Philadelphia (1981).

Estrogens, progestins and androgens are also used in animal husbandry as growth promoters for food animals. It is known in the art that compounds of these classes act as growth-promoting steroids in animals such as cattle, sheep, pigs, fowl, rabbits, etc. Delivery systems to promote the growth of animals are described, for example, in U.S. Patent 5,401,507, U.S. Patent 5,288,469, U.S. Patent 4,758,435, U.S. Patent 4,686,092, U.S. Patent 5,072,716 and U.S. Patent 5,419,910.

Specific estrogen, progestin and androgen compounds are well known to the practitioner. Especially preferred compounds belonging to this class include progesterone, estradiol benzoate and trenbolone acetate.

NSAIDS are well known in the art. The classes of compounds which belong to this group include salicylic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids (fenamates), enolic acids, and alkanones. NSAIDS exert their activity by interfering with prostaglandin biosynthesis by irreversibly or reversibly inhibiting cycloxygenase. Compounds of this group possess analgesic, antipyretic and nonsteroidal anti-inflammatory properties. Compounds belonging to these classes are described, for example, in Chapter 27 of Goodman and Gilman on pages 617 to 658 or in Ch. 22 of Foye on pages 561 to 590 as well as in U.S. Patents 3,896,145; U.S. Patent 3,337,570; U.S. Patent 3,904,682; U.S. Patent 4,009,197; U.S. Patent 4,223,299; and U.S. Patent 2,562,830, as well as the specific agents listed in The Merck Index. This invention contemplates those compounds that are oil-soluble.

Oil-soluble NSAIDS are also well known to the practitioner. Classes of NSAIDS which are preferred are indole and indecene acetic acids and heteroaryl acetic acids. Especially preferred compounds include indomethacin, ketorolac, caprofen, flunixin, ketoprofen, meloxicam, naproxen, and phenylbutazone.

COX-2 inhibitors are an especially preferred class of NASIDS. As with other NASIDS, COX-2 inhibitors are effective in treating cycloxygenase mediated diseases such as inflammation, analgesia and fever. These compounds are especially effective in treating cancer, rheumatoid arthritis and osteoarthritis. These compounds have the advantage of not affecting the integrity of the gastrointestinal tract and the renal blood flow. Examples of these compounds include (methylsulfonyl)phenyl-2-5(H)-furanone derivatives. These derivatives are described, for example, in copending application USSN 09/097,537, now allowed, which in turn is a CIP of application USN 08/728,512, filed on October 9, 1996, which in turn is based upon provisional applications nos. 60/005,371 and 06/011,673. Especially preferred COX-2 inhibitors include 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one or 3-(cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one or pharmaceutically acceptable salts or hydrates of these compounds. An especially preferred COX-2 inhibitor is polymorphic form B of 3-(cyclopropylmethoxy)-4-[4(methylsulfonyl)phenyl]-5,5-dimethyl-5H-furan-2-one.

Polymorph B may be characterized by the following parameters :

cristalline system	Trigonal
space group	R-3
description	hexagonal
unit-cell dimensions	
a (Å)	18.183
b (Å)	18.183
c (Å)	26.950
α (°)	90
β (°)	90
γ (°)	120
unit-cell volume ($Å^3$)	7716.5
number of molecules per unit-cell Z	18
Temperature of measurement (°K)	293
calculated specific gravity	1.303
weight absorption coefficient (cm^{-1})	2.11

Polymorph B may be further be characterized by the following X-ray diffraction data calculated from crystalline structure.

Table 1 : Powder X-Ray Diffraction Data calculated from crystalline structure

d(Angs)	Intensity
13,596	w
10,238	w
9,092	s
8,983	m
7,558	vw
6,798	vw
6,39	m
6,39	vw
6,194	vw
5,812	m
5,812	w
5,444	w
5,444	vw
5,249	s
5,119	s

d(Angs)	Intensity
3,209	vw
3,195	w
3,195	vw
3,184	m
3,184	vw
3,179	vw
3,128	vw
3,067	vw
3,031	vw
3,001	vw
3,001	vw
2,994	vw
2,958	vw
2,958	vw
2,932	vw

5,1	vw
4,546	vw
4,532	s
4,532	s
4,492	m
4,461	m
4,448	w
4,311	vw
4,311	vw
4,155	s
4,155	m
4,056	vw
4,056	vw
4,027	vw
4,027	vw
3,995	m
3,995	w
3,895	w
3,74	vw
3,665	vw
3,665	vw
3,581	m
3,489	vw
3,489	vw
3,459	vw
3,436	vw
3,436	vw
3,413	w
3,413	vw
3,399	vw
3,393	m
3,393	vw
3,233	vw
3,209	w

2,906	vw
2,906	vw
2,888	vw
2,853	vw
2,844	vw
2,813	vw
2,768	vw
2,753	vw
2,729	vw
2,729	vw
2,722	vw
2,722	vw
2,719	vw
2,667	w
2,667	vw
2,634	vw
2,624	vw
2,608	vw
2,522	vw
2,519	vw
2,519	vw
2,512	vw
2,504	vw
2,504	vw
2,501	vw
2,464	vw
2,464	vw
2,455	vw
2,438	vw
2,428	vw
2,428	vw
2,417	vw
2,364	vw
2,339	vw
2,301	vw

By way of comparison, the parameters and the X-ray diffraction data calculated from crystalline structure of polymorph A are reported hereunder :

TABLE 2 – Powder X-Ray Diffraction Data for Single crystal Polymorph A

d(A)	intensity
14,20	m
10,09	s
9,88	s
6,97	vw
5,33	m
5,09	w
5,09	vw
5,08	m
4,94	m
4,78	w
4,78	m
4,78	m
4,73	m
4,45	m
4,33	m
4,33	m
4,33	m
4,32	m
4,20	vw
4,20	w
4,04	w
3,81	w
3,81	vw
3,79	vw
3,75	w

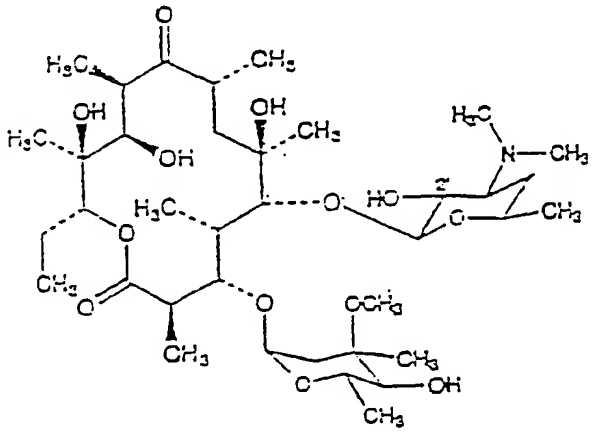
d(A)	intensity
3,72	m
3,72	m
3,70	w
3,70	w
3,67	w
3,67	w
3,60	w
3,58	w
3,58	w
3,55	w
3,51	w
3,49	vw
3,39	m
3,39	m
3,32	vw
3,29	w
3,13	vw
3,11	w
2,94	vw
2,86	vw
2,86	vw
2,85	w
2,82	vw
2,63	w
2,31	vw

The powder X-ray diffraction pattern of polymorphs A and B is represented in figures 6 and 7, respectively.

Compounds which inhibit gastric acid secretion in the stomach or act as proton pump inhibitors are well known to the practitioner and are also provided for in the present invention. These compounds include 2-(2-benzimidazolyl-pyridines) and their salts. Such

compounds are described, for example in EP 005 129, U.S. Patent 4,255,431 as well as in U.S. Patent 5,629,305. These compounds are also known to treat Helicobacter infections, U.S. Patent 5,093,342, and to act as synergists when combined with an acid degradable antibiotic, see e.g. U.S. 5,629,305. These synergistic combinations may also be formulated in the pastes of the present invention. Omeprazole or its salts is an especially preferred compound.

Macrolide antibiotics are also preferred therapeutic agents. Macrolides as a class include the erythromycin and its derivative as well as other derivatives such as the azalides. Erythromycin (MW 733.94 daltons) is the common name for a macrolide antibiotic produced by the growth of a strain of Streptomyces erythreous. It is a mixture of three erythromycins, A, B and C consisting largely of erythromycin A which is represented by the formula:



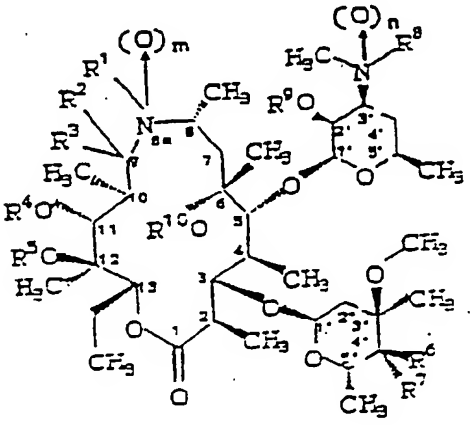
Its chemical name is (3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*, 13S*,14R*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexapyranosyl]oxy]oxacyclotetradecane-2,10-dione, ($C_{37}H_{67}NO_{13}$).

Erythromycin has a broad and essentially bacteriostatic action against many Gram-positive and some Gram-negative bacteria as well as other organisms including mycoplasmas, spirochetes, chlamydiae and rickettsiae. In humans, it finds usefulness in the

treatment of a wide variety of infections. It finds wide application in veterinary practice in the treatment of infectious diseases such as pneumonias, mastitis, metritis, rhinitis, and bronchitis in, for example, cattle, swine and sheep.

Other derivatives of erythromycins include carbomycin, clarithromycin, josamycin, leucomycins, midecamycins, mikamycin, miokamycin, oleandomycin, pristinamycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, tylosin, troleandomycin, and virginiamycin. As with the erythromycins, many of these derivatives exist as component mixtures. For example, carbomycin is a mixture of carbomycin A and carbomycin B. Leucomycin exists as a mixture of components A_1, A_2, A_3, A_5, B_1-B_4, U and V in various proportions. Component A_3 is also known as josamycin and leucomycin V is also known as miokomycin. The major components of the midecamycins is midecamycin A and the minor components are midecamycins A_2, A_3 and A_4. Likewise, mikamycin is a mixture of several components, mikamycin A and B. Mikamycin A is also known as virginiamycin M_1. Pristinamycin is composed of pristinamycins I_A, I_B, and I_C, which are identical to virginiamycins B_2, B_{13} and B_2 respectively, and pristinamycin II_A and II_B, which are identical to virginiamycin M_1 and 26,27-dihydrovirginiamycin M_1. Spiramycin consists of three components, spiromycin I, II, and III. Virginiamycin is composed of virginiamycin S_1 and virginiamycin M_1. All these components may be used in this invention. Sources of these macrolides are well known to the practitioner and are described in the literature in references such as "The Merck Index," 12th ed., S. Budarari, ed., Merck & Co., Inc., Whitehouse Station, NJ (1996).

Azalides are semisynthetic macrolides antibiotics related to erythromycin A and exhibit similar solubility characteristics. This class includes compounds of the general structure



and the pharmaceutically acceptable salts and esters thereof, and the pharmaceutically acceptable metal complexes thereof, wherein

R^1 is hydrogen;

hydroxy;

C_{1-4} alkoxy;

formyl;

C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, aryloxycarbonyl, C_{1-10} aralkoxycarbonyl, C_{1-10} alkylsulfonyl, or arylsulfonyl wherein said C_{1-10} alkyl group or aryl group is unsubstituted or substituted by 1-3 halo (F, Cl, Br). hydroxy, amino, C_{1-5} acylamino or C_{1-4} alkyl groups; or

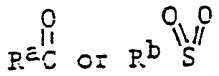
unsubstituted or substituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl wherein said substituents are independently 1-3 of

(a) aryl or heteroaryl optionally substituted by 1-3 halo (F, Cl, Br, I), C_{1-4} alkyl, C_{1-3} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl) amino or hydroxy,

(b) heterocyclyl optionally substituted by hydroxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbonyloxy or C_{1-4} alkylcarbonylamino,

(c) halo (F, Cl, Br or I),

(d) hydroxy optionally acylated by a group



wherein

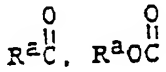
R^a is hydrogen, C_{1-6} alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl and

R^b is C_{1-6} alkyl or aryl,

(e) C_{1-10} alkoxy,

(f) aryloxy or heterocaryloxy optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,

(g) amino or C_{1-10} alkylamino optionally acylated by a group



or R^bSO_2, wherein

R^a and

R^b are as defined above,

(g) di(C_{1-10} alkyl)amino,

(h) arylamino, heteroarylamino, aralkylamino or heteroarylakylamino wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,

(i) mercapio,

(j) C_{1-10} alkylthio, alkylsulfinyl or alkylsulfonyl, arylthio, arylsulfinyl or arylsulfonyl wherein said aryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,

(k) formyl,

(l) C_{1-10} alkylcarbonyl,

(m) arylcarbonyl, heteroarylcarbonyl, aralkylcarbonyl or heteroarylalkylcarbonyl wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,

(n) carboxy,

(o) C_{1-10} alkoxycarbonyl,

(p) aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl or heterozrylalkoxycarbonyl wherein said aryl or heteroaryl group is

optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,

(q) carbamoyl or sulfamoyl wherein the N-atom is optionally substituted by 1-2 C_{1-6} alkyl groups or by a C_{4-6} alkylene chain,

(r) cyano,

(s) isonitrilo,

(t) nitro,

(u) azido,

(v) iminomethyl optionally substituted on nitrogen or carbon with C_{1-10} alkyl,

(w) oxo, or

(x) thiono;

wherein said alkyl chain, if more than two carbons in length, can be optionally interrupted by 1-2 oxa, thia or aza (-NR-wherein R is hydrogen or C_{1-3} alkyl) groups.

R^{10} is hydrogen or

R^1 and R^{10} together are C_1-C_3 alkylene optionally substituted by an oxo group;

R^1 and R^4 together are C_1-C_3 alkylene optionally substituted by an oxo group

R^2 and R^3 are hydrogen, C_{1-10} alkyl, aryl

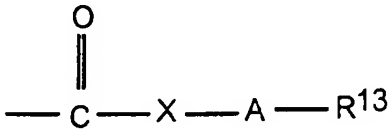
R^2 and R^3 together are oxo and thiono;

R^4 and R^5 are independently hydrogen and alkylcarbonyl;

R^4 and R^5 are together carbonyl;

R^6 and R^7 are both hydrogen or one of R^6 and R^7 is hydrogen and the other is hydroxy, an acyloxy derivative taken from the group consisting of formyloxy, C_{1-10} alkylcarbonyloxy, arylcarbonyloxy and aralkylcarbonyloxy, or

$-NHR^{12}$ wherein R^{12} is hydrogen, arylsulfonyl or heteroarylsulfonyl optionally substituted by 1-3 halo or C_{1-3} alkyl groups, alkylsulfonyl, or



where

X is a connecting bond, O or NH,

A is a connecting bond or C_1-C_3 alkylene

R^{13} is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, heteroaryl, heterocyclyl, or C_3-C_7 cycloalkyl, any of which R^{13} groups other than hydrogen can be substituted by one or more of halogen, hydroxyl, C_1-C_3 alkoxy, cyano, isonitrilo, nitro, amino, mono- or di-(C_1-C_3)alkylamino, mercapto, C_1-C_3 alkylthio, C_1-C_3 alkylsulfinyl, C_1-C_3 alkylsulfonyl, arylthio, arylsulfinyl, sulfamoyl, arylsulfonyl, carboxy, carbamoyl, C_1-C_3 alkylcarbonyl, or C_1-C_3 alkoxycarbonyl;

R^6 and R^7 are together oxo, hydroxyimino, alkoxyimino, aralkoxyimino or aminoimino;

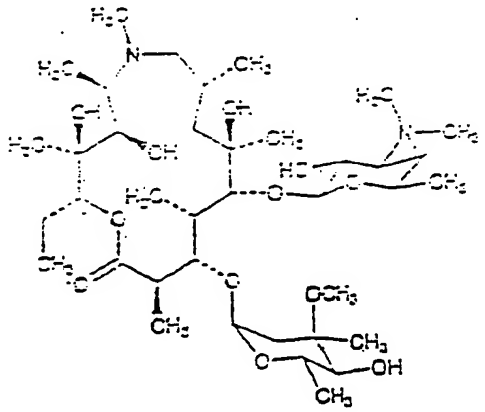
R^8 is methyl, aralkoxycarbonyl, and arylsulfonyl;

R^9 is hydrogen, formyl, C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, and arylalkoxycarbonyl;

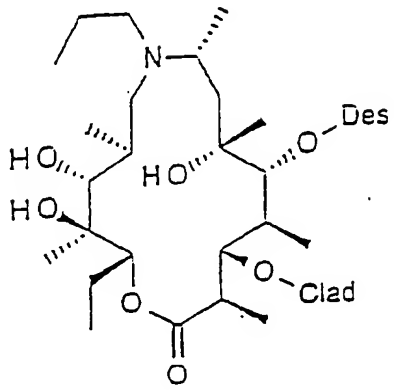
m and n are independently integers of zero or one; and said metal complex is taken from the group consisting of copper, zinc, cobalt, nickel and cadmium.

These compounds are disclosed in EP 568 699, herein incorporated by reference. Azalides as a class of components is well-known in the art and further derivatives are described, for example, in U.S. Patent Nos. 5,869,629; 5,629,296; 5,434,140; 5,332,807; U.S. 5,250,518; 5,215,890; and 5,210,235, all incorporated herein by reference.

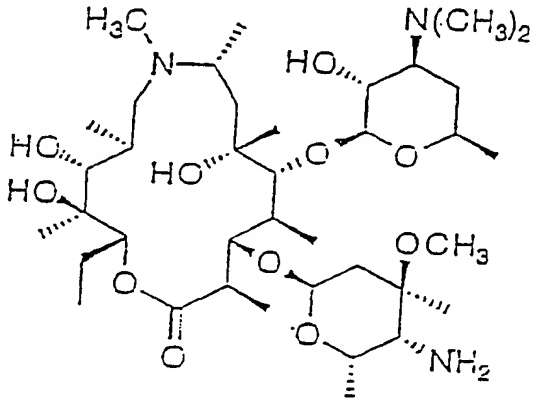
Particularly preferred is azithromycin. The structure of azithromycin is



Compounds termed herein formula I and formula II have the following structures:



wherein Des is desosomine and Clad is cladinose (formula I) and



(formula II). The compound of formula II are also known as 8a-azalide. These compounds are disclosed in EP 508 699, herein incorporated by reference. The corresponding basic and acid addition salts and ester derivatives of the macrolides, including the azalides compounds, are also contemplated. These salts are formed from the corresponding organic or inorganic acids or bases. These derivatives include the customary hydrochloride and phosphate salts as well as the acetate, propionate and butyrate esters. These derivatives may have different names. For example, the phosphate salt of oleandomycin is matromycin and the triacetyl derivative is troleandomycin. Rokitamycin is leucomycin V 4-B-butanoate, 3B-propionate.

The term "therapeutic agent" also includes the pharmaceutically or veterinary acceptable acid or base salts, where applicable, of these compounds. The term "acid" contemplates all pharmaceutically or veterinary acceptable inorganic or organic acids. Inorganic acids include mineral acids such as hydrohalic acids, such as hydrobromic and hydrochloric acids, sulfuric acids, phosphoric acids and nitric acids. Organic acids include all pharmaceutically or veterinary acceptable aliphatic, alicyclic and aromatic carboxylic acids, dicarboxylic acids tricarboxylic acids and fatty acids. Preferred acids are straight chain or branched, saturated or unsaturated C_1-C_{20} aliphatic carboxylic acids, which are optionally substituted by halogen or by hydroxyl groups, or C_6-C_{12} aromatic carboxylic acids. Examples of such acids are carbonic acid, formic acid, fumaric acid, acetic acid, propionic acid, isopropionic acid, valeric acid, α-hydroxy acids, such as glycolic acid and lactic acid, chloroacetic acid, benzoic acid, methane sulfonic acid, and salicylic acid. Examples of dicarboxylic acids include oxalic acid, malic acid, succinic acid, tataric acid and maleic acid. An example of a tricarboxylic acid is citric acid. Fatty acids include all pharmaceutically or veterinary acceptable saturated or unsaturated aliphatic or aromatic carboxylic acids having 4 to 24 carbon atoms. Examples include butyric acid, isobutyric acid, sec-butyric acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and phenylsteric acid. Other acids include gluconic acid, glycoheptonic acid and lactobionic acid.

The term "base" contemplates all pharmaceutically or veterinary acceptable inorganic or organic bases. Such bases include, for example, the alkali metal and alkaline earth metal salts, such as the lithium, sodium, potassium, magnesium or calcium salts. Organic bases include the common hydrocarbyl and heterocyclic amine salts, which include, for example, the morpholine and piperidine salts.

The ester and amide derivatives of these compounds, where applicable, are also contemplated. Specific compounds which belong to these classes of therapeutic agents are well known to the practitioner of this art.

An important feature of the present invention is the combination of a viscosity modifier to the formulation. The addition of the viscosity modifier provides for a paste formulation which contains less fumed silica than the amount normally used in a conventional paste. The inventive formulation allows for all the air that is introduced into the formulation by the fumed silica to escape when the viscosity is low. The viscosity modifier is then added to bring the viscosity of the paste to the desired level without the introduction of more air into the final product. While not wishing to be bound by theory, it is believed that because of their functional groups, the viscosity modifiers act as crosslinkers and extend the three-dimensional network formed by the interaction of the silica and the hydrophobic carrier. The viscosity modifiers also extend the crosslinking density in the formulation.

Especially preferred hydroxy-containing viscosity modifiers include PEG 200, PEG 300, PEG 400, and PEG 600. Other hydroxyl-containing viscosity modifiers include block copolymer mixtures of polyoxyalkylene compounds, i.e., poloxamers including ethylene oxide and propylene oxide poloxamer mixtures, such as those described in U.S. Patent Nos. 4,343,785; 4,465,663; 4,511,563; and 4,476,107, the disclosures of which are hereby incorporated herein by reference. Commercial versions of these nonionic poloxamer surfactants are available from BASF - Wyandotte Co., Wyandotte, Mich. and include various Pluronics such as Pluronic L81, Pluronic F108, and F127 and those Pluronics described in "Pluronic & Tetronic Surfactants", BASF Corp., 1987, as well as in "The Merck Index", 10th ed.. on page 1090 and in Remington Pharmaceutical Science. Other suitable density modifiers useful as of the present invention

include: polyoxyethylene sorbit in monoleate (Polysorbate 80); polyethylene glycols (Pluracols); nonylphenol ethoxylates (Surfonics); and linear alcohol ethoxylates polyethyleneglycol paraisooctypheny/ethers (Tritons's).

Propylene glycol mono- and di-fatty acid esters are also provided for in the inventive formulations. These esters include, for example, propylene glycol dicaprylate; propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, and propylene glycol stearate, most preferably propylene glycol caprylic-capric acid diester as is available under the Trade Name MIGLYOL 840.

Other compounds which function as viscosity modifiers are those which contain both hydroxy and amino function groups. Such compounds include, for example, monoethanolamine, diethanolamine and triethanolamine. These compounds, as well as their use, are well known to a practitioner in the pharmaceutical and veterinary arts.

The amount of viscosity modifier varies from formulation to formulation and the determination of the amount required is well within the routine skill of a practitioner in the formulation art. Preferred is about 0.01 to about 20% of viscosity modifier, based upon total weight of the composition. An especially preferred amount is about 0.05 to about 5%, with about 0.1 to about 2% being most preferred.

Fumed silica is used as the thickening agent. In the pastes according to this invention, the amount of fumed silica is very low. This allows an intermediate with a low viscosity, which in turn allows for a quick escape of the air by buoyancy. After letting the intermediate settle for about 10 minutes, no air was detected in the intermediate. Preferred pastes comprise from about 1 to about 20%, based upon total weight of solution, with from about

1% to about 6% being preferred. Amounts of about 0.02% to about 20%, about 1% to 6.5% or about 1 to about 4% or 5% are also preferred. A paste where the amount of silica is about 4.25% is especially preferred.

The carrier is another important component of the formulation. It is the liquid phase that dissolves the active drug to give an excellent content uniformity and bioavailability. Compounds which act as carriers include solvents that are suitable for pharmaceutical applications, such as triacetin, short to medium chain mono-, di-, or tri-glycerides, glycerin, water, propylene glycol, N-methyl pyrrolidinone, glycerol formal, polyethylene glycol, polyethylene glycol-polypropylene glycol-polyethylene glycol tri-block copolymers, vegetable oil, sesame oil, soybean oil, corn oil, mineral oil, peanut oil, castor oil, cotton oil, transcutol, benzyl alcohol, N, N-dimethylformamide, dimethylsulfoxide, or the like. These compounds may be used alone or as mixtures. Triacetin is especially preferred as it has some water solubility that allows an easy cleaning of the manufacturing equipment. Unlike some aqueous based pastes, triacetin does not support microbial growth, which eliminates the need for a preservative. Mixtures of other carriers with triacetin are also preferred. The amount and type of hydrophobic carrier for a particular formulation is well within the skill level of the practitioner.

When present, any of the conventional pharmaceutical or veterinary colorants may be used. Such colorants include, for example, dyes, aluminum lakes, colorants based upon iron oxide, caramel or combinations of various colorants. Preferably up to about 20%, by weight of total composition, may be present with about 0.001 or 0.01% to about 10% and 0.001 to about 4% being most preferred.

Absorbents may also be added to the paste formulation. Such compounds are well known in the art to the practitioner as well as their use in pastes. These compounds

effectively prevents or alleviates the phase separation of the product during storage. Preferred absorbents include magnesium carbonate, calcium carbonate, starch, cellulose and its derivatives, or mixtures of absorbents with magnesium carbonate being especially preferred. The inclusion of these compounds is optional with amounts of 0% to about 30%, 0 to about 15% or about 1% to about 15% or about 1% to about 10%, based on total weight of the composition being especially preferred.

In addition to the therapeutic agent, the viscosity modifier, and the carrier, the formulation can contain other inert ingredients such as antioxidants, preservatives, stabilizers or surfactants. These compounds are well known in the formulation art. Antioxidant such as an alpha tocopheral, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0%, based upon total weight of the formulation. Preservatives such as the parabens (methylparaben and/or propylparaben) are suitably used in the formulation in amounts ranging from about 0.01 to about 2.0%. Other preservatives include benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, and the like.

Surfactants can also be added to help solublize the active drug, to prevent crystallization, and to prevent phase separation. Some examples of the surfactants are: glyceryl monooleate, polyoxyethylene sorbitan fatty acid esters, sorbitan esters, polyvinyl alcohol,

Pluronics, sodium lauryl sulfate, etc. Again, these compounds, as well as their amounts are well known in the art.

The instant formulation is equally applicable to other compounds used for pastes as long as such compounds are soluble in the carrier. Additional compounds that can be used in this formulation are other antiparasitic agents and antibiotics, therapeutic vitamin and mineral supplements, and other agents that are assisted in their therapeutic effect by having improved stability over a prolonged period of time. Again, such compounds would be well known to the practitioner.

The pastes are administered to a warm-blooded animals, such as humans, cattle, sheep, pigs, cats, dogs, horses, and the like, by oral, topical, dermal and subdermal administration. The inventive pastes may also be administered to humans. The amount of therapeutic agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner. Generally, such preparation normally contain about 0.0005 to about 50% of therapeutic agent by total weight of composition. Preferred formulations are those containing about 0.01 to 10% of therapeutic agent and especially preferred formulations are those containing about 2.5 to about 5% of therapeutic agent. Other preferred amounts include about 0.1 to about 0.01 to about 50% or about 10% or about 0.5 to about 3%. For the avermectins and milbemycins, the formulations will generally be prepared to administer from about 0.1 to about 2 mg/kg, preferably from about 0.4 to about 0.85 mg/kg and most preferably from about 0.6 to about 0.7 mg/kg of the active ingredient. At a preferred dose volume of about 1 ml to treat 50 kg of animal body weight the formulation contains from about 5 to about 50 mg of the active agent per ml of solution or about 0.5 to about 10%, preferably about

2.5 to about 5% w/v. However depending upon the activity of the compound and the animal being treated, doses as low as about 0.3% of the active ingredient are usable. For nodulisporic acid and its derivatives, a formulation containing about 0.0005 to about 5% of the active compound is preferred.

The present invention also provides for a process to prepare paste formulations which is easier and relatively inexpensive. Because fumed silica is a relatively expensive and difficult to handle material, the use of a density modifier reduces the overall cost of the product and minimizes the material handling issue. The manufacturing process is described as follows:

1. In a proper mixer, charge all or a portion of the carrier. Add the active drug and mix it until all of the drug is dissolved.
2. Add the colorant and magnesium carbonate, if necessary. Apply appropriate mixing action to uniformly disperse the titanium dioxide and magnesium carbonate.
3. Add fumed silica to the mixer in a single charge or in portions. Apply appropriate mixing action to uniformly disperse the fumed silica.
4. Add the remaining portion of the triacetin to the mixer. Apply appropriate mixing action to produce a uniform intermediate.
5. Let the intermediate settle for a proper amount of time to let the air that was entrapped with the addition of fumed silica to escape.
6. Add the viscosity modifier and mix until a uniform paste product is produced.

In comparison, with the process to prepare prior paste products, such as EQVALAN paste and GASTROGARD paste, which are manufactured using different formulations and processes, this invention has the following advantage. First, the process is

much simpler. A 300 kg batch can be made in less than 2 hours, while 5 hours or more are needed for EQVALAN and GASTROGARD pastes. Second, no heating or cooling is required during the manufacturing of this product, which lowers the equipment demand and cost. Many other paste products require heating and/or cooling. Third, this product is not very shear-sensitive. During manufacturing, over mixing of the inventive pastes, to a certain extent, has little effect on the final consistency of the product. This robustness provides for a forgiving manufacturing process. Many other paste products are shear sensitive and careful manufacturing parameter must be maintained to assure product quality. Fourth, the inventive pastes exhibit little temperature sensitivity. Extended storage under accelerated storage condition showed little physical or chemical change. While many other paste products change the viscosity, and/or dry out, and/or separate significantly when stored under high (e.g. 60°C)/or low (e.g. -20°C) temperature conditions.

The inventive paste formulations may be used to treat a number of disease states by administering to the host in need thereof an effective amount of the paste containing the therapeutic agent. The determining of a treatment protocol of a specific indication would be well within the skill level of a practitioner in the pharmaceutical or veterinary arts. Disease states which may be treated by the inventive formulations include, for example, treating inflammation, treating osteoarthritis and rheumatoid arthritis pain or fever, treating or preventing insect or parasitic infestations, treating or preventing bacterial infections; or inhibiting excess acid secretions in the stomach for treating stomach ulcers. The hosts include all animals, e.g. cats, dogs, cattle, sheep, horses, pigs, and humans.

EXAMPLES

A better understanding of the present invention and of its many advantages will be had from the following examples, given by way of illustration.

Example 1

The penetration value of placebo pastes were determined in order to demonstrate the ability of the viscosity modifier to increase the viscosity of the paste at low values of fumed silica. Penetration pastes containing 4% CAB-O-SIL and 0.25% to 2% of a viscosity modifier were prepared in a mixed vehicle (triacetin: miglyol 840). The penetration values of the resulting composition are listed below.

Table 4 Penetration value of placebo paste (mm)

Viscosity modifier	Initial	10 days at 50°C	1 month at 50°C
MEA 0.25%	23.4	22.7	23.7
MEA 0.5%	25.2	25.8	25.3
MEA 1.0%	24.3	22.7	21.9
MEA 1.5%	28.1	23.8	26.2
TEA 0.5%	25.6	21.9	20.7
Tween 80 1%	32.0	20.5	21.2
PEG 300 1%	33.4	26.6	26.5
PEG 300 2%	38.4	26.1	29.1
Pluronic L81 1%	43.9	27.0	27.0
None	Too thin to be tested (>65)	38.9	42.2

After two months storage at room temperature, pastes changed to pale yellow when MEA was added. Degree of yellowish: MEA 1.5%> MEA 1.0%> MEA 0.5%> MEA 0.25%. No significant color change in pastes with other additives. Also paste with MEA had an acidic smell, while other pastes did not have.

In the table, MEA is the abbreviation for monoethanolamine and TEA is the abbreviation for triethanolamine. The results demonstrate that the viscosity modifiers have the ability to increase dramatically the viscosity of the placebo paste at low CAB-O-SIL levels. The results in Table 6 also demonstrate that the viscosity of all the pastes increased slightly over time. This result is consistent with the data presented in Fig. 2 which demonstrate that after

storage for 6 days at 60°C the viscosity increased slightly. From this data, one would expect that this increase would stop after a few days.

Example 2

The physical stabilities of three pastes according to the present invention were prepared and placed into a 6.1 ml white syringe. The formulations were as follows:

Table 5 Paste formulation containing the COX-2 inhibitor, formula III

	Formula A	Formula B	Formula C
Cox-2 inhibitor[a]	1.16%	1.16%	1.16%
CAB-O-SIL	3.5%	4.0%	4.0%
PEG 300	----	1.0%	1.0%
Monoethanolamine	0.2%	----	----
Titanium Dioxide	----	2.0%	----
Triacetin	QS	QS	QS

[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

a. Chemical Stability

The chemical stability of these formulations was tested over accelerated storage conditions. The results of these tests are provided below in Table 4.

Table 6 Chemical stability of paste formulation containing the COX-2 inhibitor, 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

	% of initial after 10 days at 60°C	% of initial after 4 weeks at 60°C	% of initial after 4 weeks at 40°C	% of initial after 4 weeks at 40°C/75% RH
Formula A	99.3%	101%		
Formula B	98.3%	99.4%	99.0%	99.0%
Formula C	99.4%	99.4%		

From these data one may conclude that the inventive formulations would be stable for a shelf life of two years.

b. Viscosity

Most semi-solic products change viscosity over storage. A useful product viscosity needs to be maintained throughout the shelf-life of a product to ensure animal acceptance and ease of use. Since the viscosity usually changes more and faster under higher temperature, the viscosity change of Formulation A and B was studied at 60°C (Table 7).

Table 7 Viscosity change of Formulation A and B under accelerated storage conditions.

	Initial	1 wk 60°C	4 wk 60°C	4 wk 40°C	4 wk 40°C/75% RH
Formulation A	22.8	22.9	22.9		
Formulation B	23.7	17.7	15.2	18.5	18.7

Formulation A used MEA as the viscosity modifier and showed almost no change in viscosity after even 4 weeks at 60°C. Formulation B used PEG 300 as the viscosity modifier and had a slight increase in viscosity after 4 weeks at 60°C and this increase is expected to stop after longer storage. The viscosity change under 40°C/75% RH was similar to that of 40°C, indicating that the humidity had no impact on paste viscosity. In contrast to Eqvalan or Gastrogard pastes, where Thixcin R was used as the thickener and their viscosity increased from 20-40 mm to 6 mm after 4 weeks at 60°C, the viscosity increase in these formulations is insignificant.

The viscosity of these pastes at extreme use temperature has not been measured. But based on visual observation, these pastes had good consistency at a wide temperature range.

c. Whipping

Slight phase separation: comparable to that of GASTROGARD, was observed in all three formulations, with Formulation B having slightly less separation.

d. Shrinkage and Discoloration

Discoloration was not seen in pastes except those using MEA as the viscosity modifier. Formulation A (containing 0.20% MEA) changed to slightly yellow but still clear. This slight discoloration is known for MEA and it has no impact on the drug.

No shrinkage occurred to all three formulations.

e. Air Entrapment

No air entrapment was noticed in the pastes.

Example 3.

Table 8 lists the concentrations of placebo pastes prepared in order to investigate whipping:

Table 8 Placebo Pastes

Formula D	Formula E	Formula F
4% CAB-O-SIL	4.5% CAB-O-SIL	5% CAB-O-SIL
1% PEG 300	1% PEG 300	1% PEG
1% $MgCO_3$	--	--
94% Triacetin	94.5% Triacetin	94% Triacetin

Whipping (phase separation) in all these pastes was reduced with whipping almost unnoticeable in formula D.

Example 4

The viscosity change of these two pastes under accelerated conditions is shown in Table 9

Table 9 Viscosity change of placebo pastes containing 1% PEG 300 and different amounts of CAB-O-SIL under accelerated storage condition.

Formulation	CAB-O-SIL content	Initial (mm)	6 days at 60°C	14 days at 60°C
D	4.0%	34.2	27.4	----
E	4.5%	23.9	18.4	18.8
F	5.0%	21.1	13.0	11.9

The paste of Formula F with 5% CAB-O-SIL seemed to be unnecessarily over-thickened. The paste of Formula E with 4.5% CAB-O-SIL was better balanced with respect to viscosity and whipping. Moreover, Formula E seemed to provide the best viscosity over storage.

Example 5

The following paste was prepared according to the process of the present invention.

Table 10 Formulation example with a COX-2 inhibitor

Ingredient	Composition in the specific example
COX-2 inhibitor[a]	0.82%
Titanium dioxide	0.2%
Magnesium carbonate	2%
Fumed silica	4.25%
Polyethylene Glycol (PEG) 300	0.4%
Triacetin	QS

[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

A portion of the triacetin was charged into a mixer followed by the addition of the COX-2 inhibitor. The compounds were mixed until all the drug was dissolved. Next, titanium dioxide and magnesium carbonate were added. Mixing continued until the titanium dioxide and magnesium carbonate were uniformly dispersed. Subsequent to this, fumed silica was added to the mixer and mixing occurred until the fumed silica was uniformly dispersed. The remaining portion of the triacetin to the mixer. Mixing occurred until a uniform intermediate was obtained. The intermediate was allowed to settle for 10 minutes until the air that was entrapped with the addition of fumed silica escaped. PEG was added and mixing occurred until a uniform paste product was produced.

Example 6

The following paste was prepared using a process similar to that of Example 5. A uniform paste was obtained.

Table 11 Formulation example with a COX-2 inhibitor

Ingredient	Composition in the specific example
COX-2 Inhibitor[a]	1.64%
FD&C Blue #1, aluminum lake	0.005%
Magnesium carbonate	2%
Fumed silica	4.25%
Polyethylene Glycol (PEG) 300	0.4%
Triacetin	QS

[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

Example 7

The following paste was prepared using a process similar to that in Example 6. A uniform paste was obtained.

Table 12 Formulation example with a COX-2 inhibitor

Ingredient	Composition in the specific example
COX-2 inhibitor[a]	2.5%
Titanium dioxide	1%
Fumed silica	4%
Monoethanolamine	1.0%
Triacetin	50%
Miglyol 840	QS.

[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

Example 8

In order to test the robustness of the paste obtained by the inventive process, a placebo paste was prepared by the following process:

1. Charge triacetin. Turn on the mixing screw and chopper until the drug is completely dissolved.
2. Stop mixer, add titanium dioxide and turn on the chopper to disperse.
3. Stop the mixer, add CAB-O-SIL in several portions to the mixer. After each portion is added, turn on the mixer to wet the powder.
4. After all CAB-O-SIL is added, mix until uniform.
5. Stop mixer and wait for 10 minutes to let air escape.
6. Add magnesium carbonate. Add the remaining triacetin and PEG 300 to the mixer. Turn on mixing screw to mix until uniform.

To determine the robustness of the paste obtained by the inventive process, the intermediate sample (4% CAB-O-SIL in triacetin) at step 5 was tested with Brookfield viscometer (Fig. 4). Its viscosity seems to be not very sensitive to the low shear testing condition. As shown in Fig. 4, the viscosity remained almost constant throughout the course of a 5 minute measuring in the testing container. To evaluate the shear sensitivity of the end product, the final paste at step 6 was subjected to high shear using a homogenizer at 2500 rpm. Samples were collected at different time intervals and tested using Brookfield viscometer and penetrometer (Fig. 5). Both the Brookfield testing and penetrometer testing of the initial end product and the aged end product at 60°C demonstrated that the paste at step 6 were only a little sensitive to shear. Based on these data, we conclude that over-mixing during production should not have much impact on the paste viscosity.

Example 9 : Conversion of polymorph A to polymorph B by stirring in methanol without seeding

To a 5 ml flask was added 1 g of methanol and 1.5 g of polymorph A.

The agitation was maintained at room temperature for 50 minutes. All polymorph A had converted to polymorph B after this time. The results on the polymorphic form were confirmed by X-Ray diffraction.

The polymorphic B form may be formulated as described in examples 5-7.

The above description of the invention is intended to be illustrative and not limiting. Various changes or modifications in the embodiment described may occur to those skilled in the art. These can be made without departing from the scope or spirit of the invention.

What is claimed is:

1. A pharmaceutical or veterinary paste formulation comprising:

(a) an effective amount of a therapeutic agent;

(b) fumed silica;

(c) a viscosity modifier;

(d) a carrier;

(e) optionally, an absorbent; and

(f) optionally, a colorant, stabilizer, surfactant, or preservative.

2. The paste according to claim 1, which comprises:

(a) a therapeutic agent selected from the group consisting of insecticides, acaricides, parasiticides, antibiotics, growth enhancers, or oil-soluble NSAIDS;

(b) fumed silica;

(c) a viscosity modifier;

(d) an absorbent;

(e) a colorant; and

(f) a carrier which is triacetin, a monoglyceride, a diglyceride, or a triglyceride.

3. The paste formulation according to claim 3, wherein the viscosity modifier is PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxylene sorbitan monoleate, or poloxamers; the absorbent is magnesium carbonate, calcium carbonate, starch, or cellulose and its derivatives; and the colorant is titanium dioxide, dye or lake.

4. The paste formulation according to claim 1, comprising:

(a) a therapeutic agent selected from the group consisting of avermectins, milbemycins, nordulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridyl methyl derivatives, phenylpyrazoles, COX-2 inhibitors or a proton pump inhibitor.

(b) fumed silica;

(c) a viscosity modifier;

(d) an absorbent;

(e) a colorant; and

(f) a carrier which is triacetin, a monoglyceride, a diglyceride, or a triglyceride.

5. The paste formulation according to claim 4, wherein the viscosity modifier is PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxyethylene sorbiton monoleate, or poloxamers; the absorbent is magnesium carbonate, calcium carbonate, starch, or cellulose and its derivatives; and the colorant is titanium dioxide, dye or lake.

6. The paste formulation according to claim 1, which, based upon total weight of composition, comprises:

(a) about 0.01 to about 50% of a therapeutic agent;

(b) about 0.02 to about 20% fumed silica;

(c) about 0.01% to about 20% of a viscosity modifier;

(d) 0% to about 30% of an absorbent;

(e) 0% to about 20% of a colorant; and

(f) Q.S. a carrier.

7. The paste formulation according to claim 4, based upon total weight of the composition, comprises:

(a) about 0.01 to about 50% of a therapeutic agent;

(b) about 1% to about 6.5% fumed silica;

(c) about 0.05% to about 5% of a viscosity modifier;

(d) about 1% to about 10% of an absorbent;

(e) 0.01% to about 10% of a colorant; and

(f) Q.S. a carrier.

8. The paste formulation according to claim 4, wherein the therapeutic agent is an avermectin or a milbemycin.

9. The paste formulation according to claim 8, wherein the avermectin or milbemycin is ivermectin, praziquantel, abamectin, emememectin, eprinomectin, doramectin, moxidectin, or selamectin.

10. The paste formulation according to claim 5, wherein the therapeutic agent is praziquantel or selamectin.

11. The paste formulation according to claim 5, wherein the therapeutic agent is a COX-2 inhibitor.

12. The paste formulation according to claim 11, wherein the COX-2 inhibitor is 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one or 3-(cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one or pharmaceutically acceptable salts or hydrates of these compounds.

13. The paste formulation according to claim 12, wherein the COX-2 inhibitor is the polymorphic B form of 3-(cyclopropylmethoxy)-4-[4-(methylsulfonyl)phenyl-5,5-dimethyl]-5H-furan-2-one, characterized by the following parameters :

cristalline system	Trigonal
space group	R-3
description	hexagonal
unit-cell dimensions	
a (Å)	18.183
b (Å)	18.183
c (Å)	26.950
α (°)	90
β (°)	90
γ (°)	120
unit-cell volume ($Å^3$)	7716.5
number of molecules per unit-cell Z	18
Temperature of measurement (°K)	293
calculated specific gravity	1.303
weight absorption coefficient (cm^{-1})	2.11

and/or the following X-ray diffraction data calculated from crystalline structure :

d(Angs)	Intensity
13,596	w
10,238	w
9,092	s
8,983	m
7,558	vw
6,798	vw
6,39	m
6,39	vw
6,194	vw
5,812	m
5,812	w
5,444	w
5,444	vw
5,249	s

d(Angs)	Intensity
3,209	vw
3,195	w
3,195	vw
3,184	m
3,184	vw
3,179	vw
3,128	vw
3,067	vw
3,031	vw
3,001	vw
3,001	vw
2,994	vw
2,958	vw
2,958	vw

5.119	s
5,1	vw
4.546	vw
4.532	s
4.532	s
4.492	m
4,461	m
4.448	w
4,311	vw
4.311	vw
4,155	s
4.155	m
4.056	vw
4.056	vw
4.027	vw
4.027	vw
3.995	m
3.995	w
3.895	w
3.74	vw
3.665	vw
3.665	vw
3.581	m
3.489	vw
3.489	vw
3.459	vw
3.436	vw
3.436	vw
3.413	w
3.413	vw
3.399	vw
3.393	m
3.393	vw
3.233	vw
3.209	w

2,932	vw
2,906	vw
2,906	vw
2.888	vw
2,853	vw
2,844	vw
2,813	vw
2,768	vw
2,753	vw
2,729	vw
2,729	vw
2,722	vw
2.722	vw
2,719	vw
2,667	w
2.667	vw
2.634	vw
2,624	vw
2,608	vw
2,522	vw
2.519	vw
2,519	vw
2,512	vw
2,504	vw
2.504	vw
2,501	vw
2,464	vw
2.464	vw
2.455	vw
2.438	vw
2.428	vw
2,428	vw
2.417	vw
2,364	vw
2.339	vw
2.301	vw

14. The paste formulation according to claim 5, wherein the therapeutic agent is a substituted pyridylmethyl derivative or a phenylpyrazole.

15. The paste formulation according to claim 14, wherein the therapeutic agent is imidacloprid or fipronil.

16. The paste formulation according to claim 3. wherein the therapeutic agent NSAID.

17. The paste formulation according to claim 16, wherein the therapeutic agent is carprofen, flunixin, ketoprofen, meloxicam, naproxen or phenylbutazone.

18. The paste formulation according to claim 5. wherein the therapeutic agent is a proton pump inhibitor.

19. The paste formulation according to claim 18. wherein the proton pump inhibitor is omeprazole or a salt thereof.

20. The paste formulation according to claim 5. wherein the therapeutic agent is an estrogen, a progenstin, or an androgen.

21. The paste formulation according to claim 1. wherein the therapeutic agent is an insect growth regulator.

22. The paste formulation according to claim 4. which, based upon total weight of the composition, comprises:

(a) 2.5% of a therapeutic agent;

(b) 4.0 % fumed silica;

(c) 1.0% monoethanolamine;

(d) 1.0% titanium dioxide;

(e) 50.0% triacetin;

(f) 41.5% propylene glycolcaprlic-capric diester 840.

23. The paste formulation according to claim 4, which, based upon total weight of the composition, comprises:

(a) 0.82% of a therapeutic agent;

(b) 4.25% fumed silica;

(c) 2.0% magnesium carbonate;

(d) 0.20% titanium dioxide;

(e) 0.4% polyethylene glycol 300; and

(f) 92.33% triacetin.

24. The paste formulation according to claim 1, wherein the formulation is for oral administration.

25. The paste formulation according to claim 1, wherein the formulation is for topical, dermal or transdermal administration.

26. The paste formulation according to claim 1, which comprises an antioxidant and the antioxidant is selected from the group consisting of alpha tocopherol, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metobisulfate, n-propyl gallate, BHA, BHT and monothioglycerol.

27. The paste formulation according to claim 1 which comprises a preservative and the preservative and the preservative is selected from the group consisting of the parabens, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, and thimerosal.

28. A method for treating inflammation, pain, or fever which comprises administering of administering an effective amount of a paste formulation according to claim 16 to a host in need thereof.

29. The method according to claim 28, wherein the host is a horse, cattle, pig or human.

30. A method for treating inflammation, pain or fever, rheumatoid arthritis or osteoarthritis which comprises administering an effective amount of a paste formulation according to 11. to a host in need thereof.

31. The method according to claim 30. wherein the host is a horse. cattle. pig or human.

32. A method for treating or preventing insect infestation which comprises administering an effective amount of a paste formulation according to claim 14 to a host in need thereof .

33. The method according to claim 32. wherein the insects are fleas.

34. A method for treating or preventing parasitic infestations in a host in need thereof. which comprises administering a paste formulation according to claim 8 to a host in need thereof.

35. The method according to claim 34. wherein the host is a horse. cattle. pig or human.

36. A method for regulating fertility in a host in need thereof. which comprises administering a paste formulation according to claim 20 to said host.

37. The method according to claim 36. wherein the host is a horse. cattle, pig or human.

38. A method for killing insects which comprises applying to said insects or an environment they reside, an effective amount of a compound according to claim 21.

39. A method for inhibiting acid secretion in the stomach of a host in need thereof which comprises administering to said host an effective amount of a paste according to claim 18.

40. A method for preventing or treating a bacterial infection of a host in need thereof which comprises administering to said host an effective amount of paste according to claim 18.

41. The paste formulation according to claim 3 wherein the therapeutic agent is an antibiotic.

42. The paste formulation according to claim 41, wherein the antibiotic is 8a-azalide, azithromycin or erythromycin.

43. A method of treating bacterial infection in a host in need thereof which comprises administering to said host an effective amount of a compound according to claim 42.

44. A process for preparing a paste formulation according to claim 1, comprising the steps of:

(a) dissolving or dispensing the therapeutic agent into the carrier by mixing;

(b) adding the fumed silica to the hydrophobic carrier containing the dissolved therapeutic agent and mixing until the silica is dispersed in the carrier;

(c) allowing the intermediate formed in (b) to settle for a time sufficient in order to allow the air entrapped during step (b) to escape; and

(d) adding the viscosity modifier to the intermediate with mixing to produce a uniform paste.

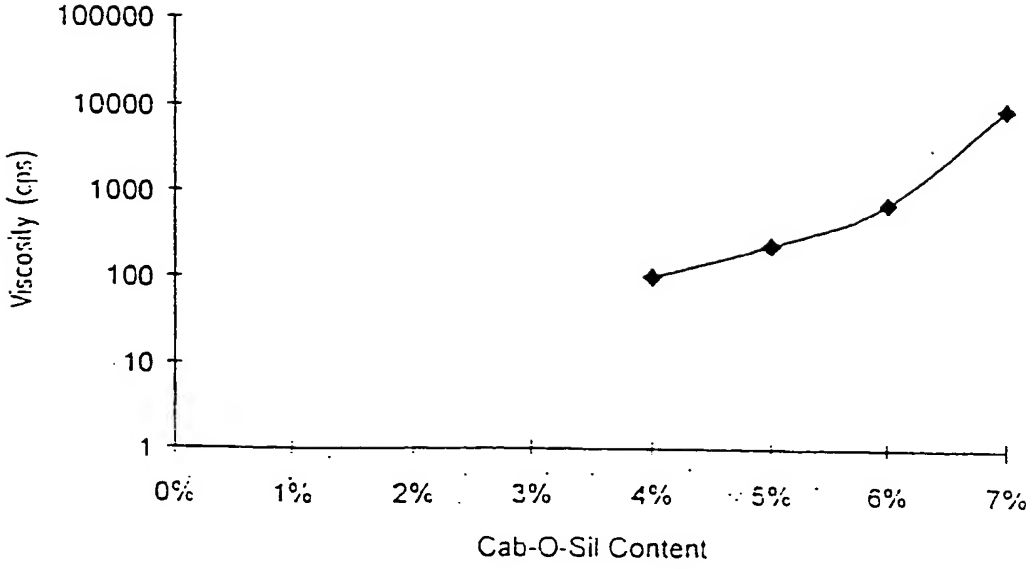

100000
10000
1000
100
10
1
Viscosity (cps)
0%
1%
2%
3%
4%
5%
6%
7%
Cab-O-Sil Content

FIG.1

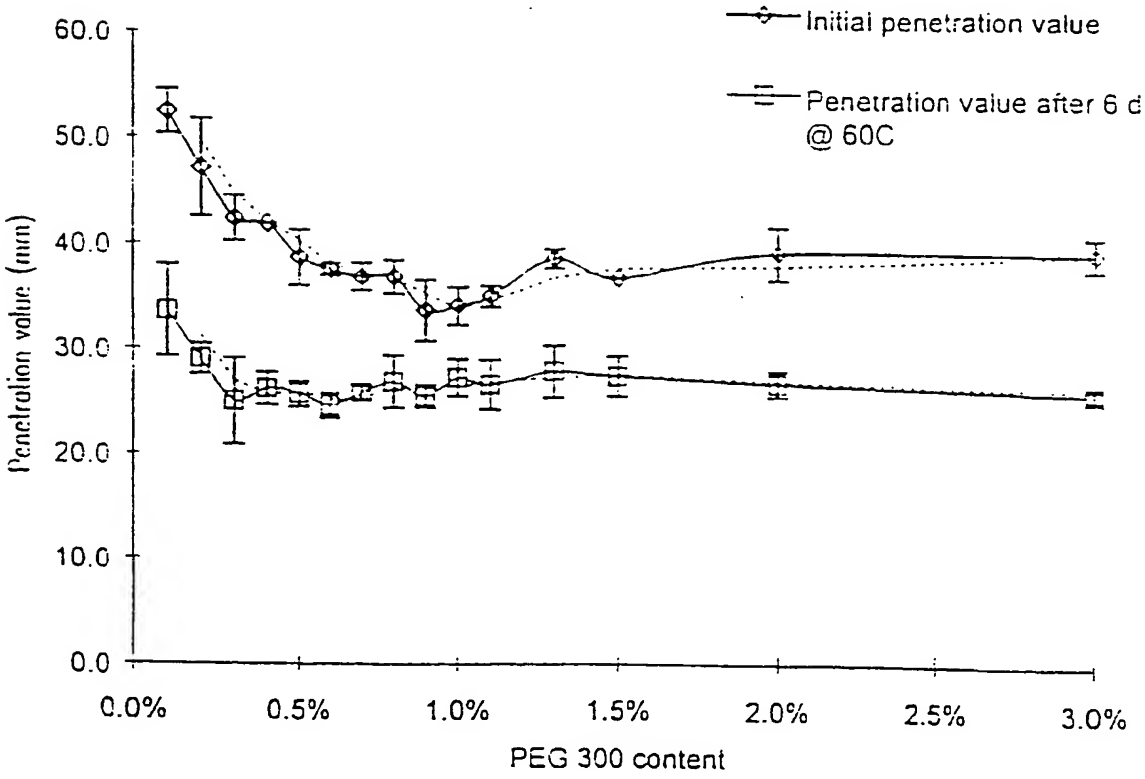

Initial penetration value
Penetration value after 6 d @ 60C
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Penetration value (mm)
0.0%
0.5%
1.0%
1.5%
2.0%
2.5%
3.0%
PEG 300 content

FIG.2

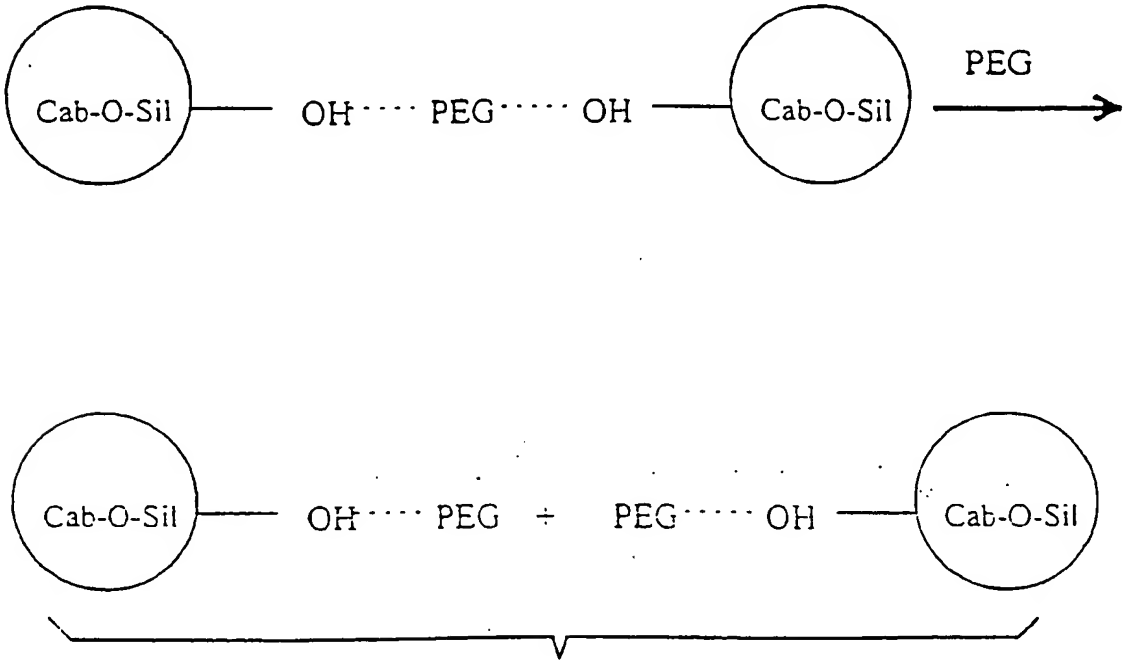

Cab-O-Sil
OH···· PEG····· OH
Cab-O-Sil
PEG
Cab-O-Sil
OH···· PEG ÷ PEG····· OH
Cab-O-Sil

FIG.3

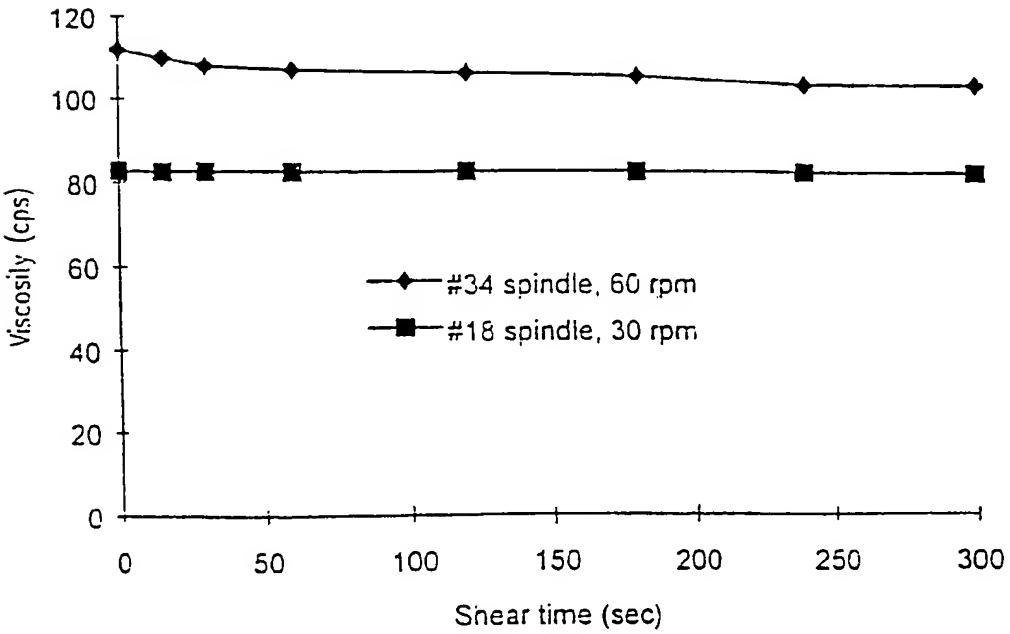

120
100
80
60
40
20
0
Viscosity (cps)
#34 spindle, 60 rpm
#18 spindle, 30 rpm
0
50
100
150
200
250
300
Shear time (sec)

FIG.4

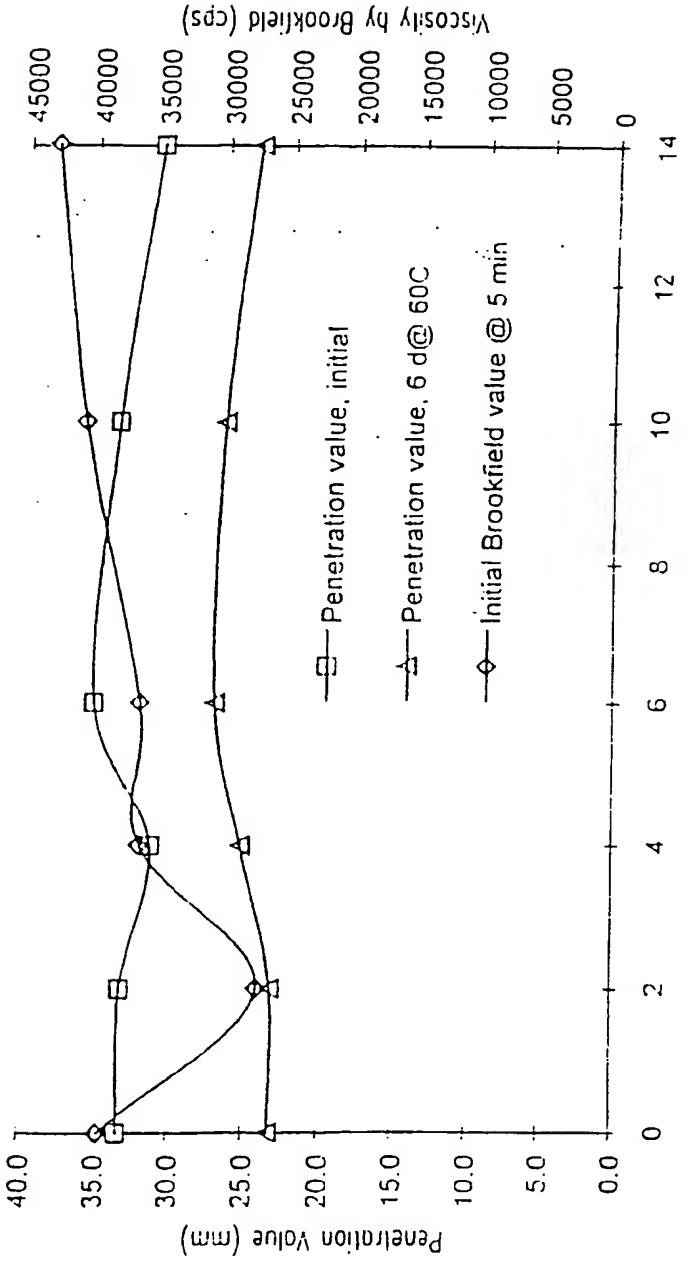

Penetration Value (mm)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Viscosity by Brookfield (cps)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0
2
4
6
8
10
12
14
Shear time at 2500 rpm (min)
Penetration value, initial
Penetration value, 6 d@ 60C
Initial Brookfield value @ 5 min

FIG.5

FIG.6

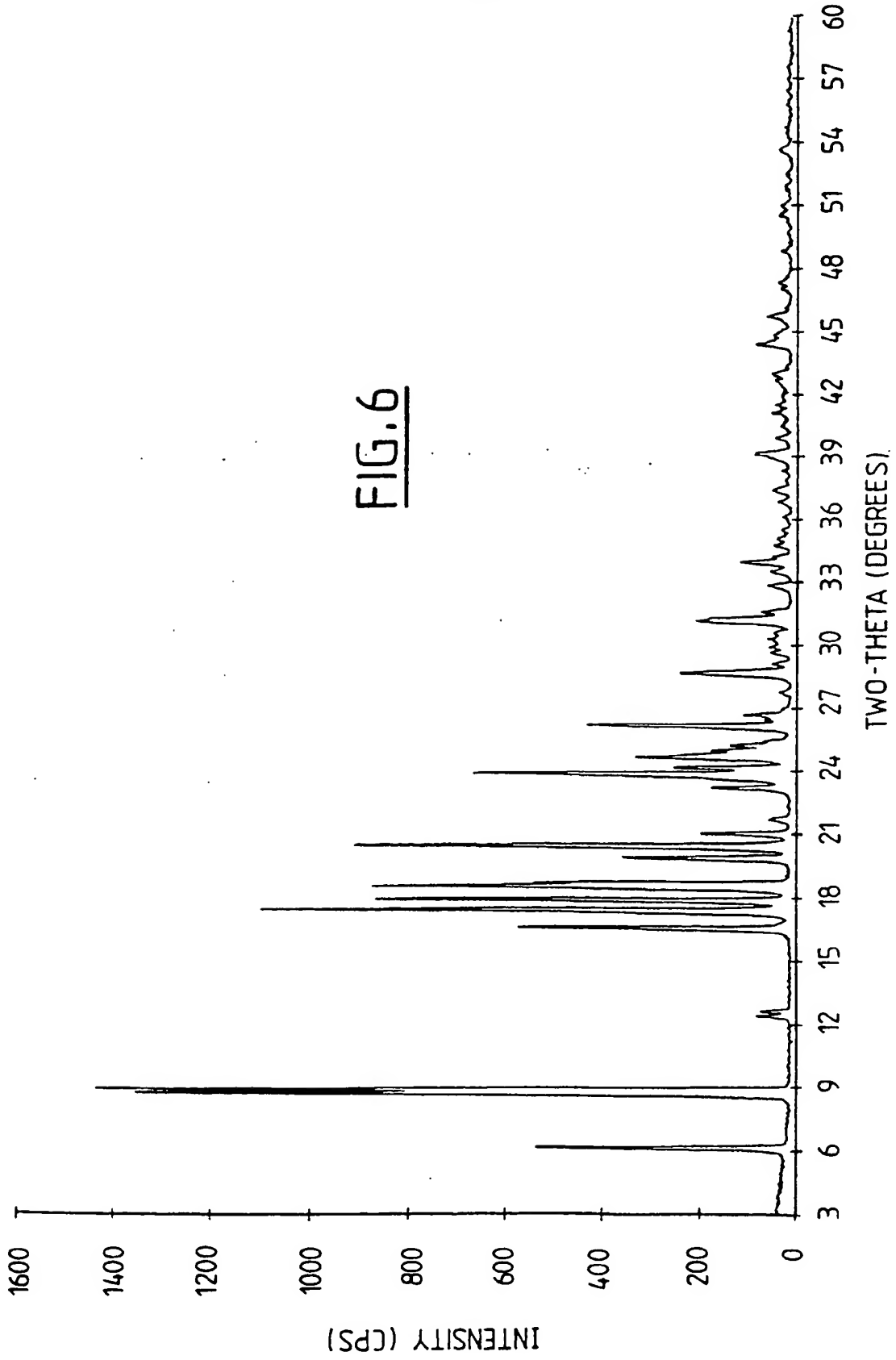
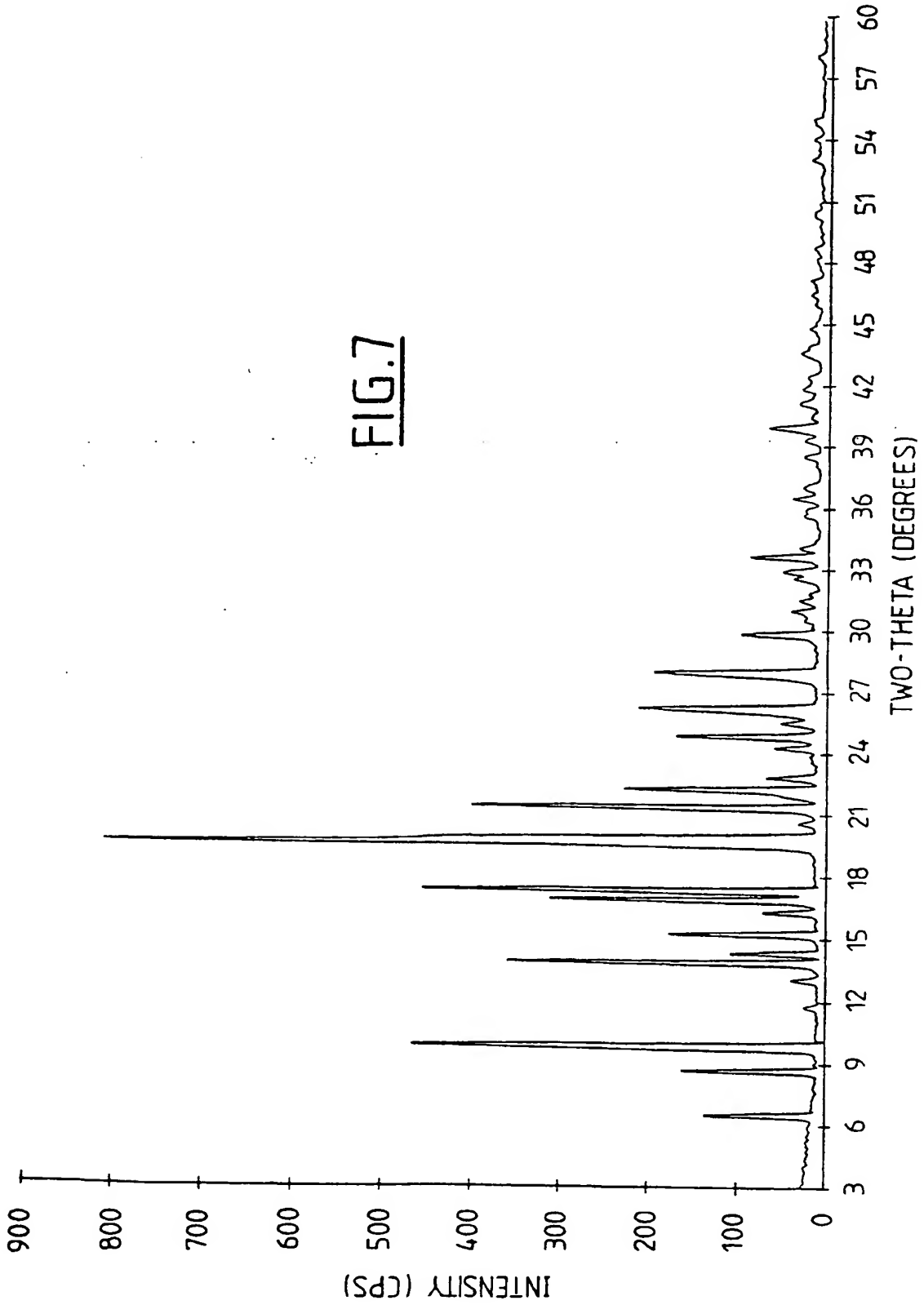

INTENSITY (CPS)
1600
1400
1200
1000
800
600
400
200
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
TWO-THETA (DEGREES)

FIG.7


INTENSITY (CPS)
900
800
700
600
500
400
300
200
100
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
TWO-THETA (DEGREES)

INTERNATIONAL SEARCH REPORT

Ir. ..ational Application No
PCT/EP 01/01155

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/02 A61K47/18 A61K47/26 A61K47/34 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 181 525 A (AMERICAN CYANAMID CO) 21 May 1986 (1986-05-21) example 1 ---	1,24,25
X	US 5 122 377 A (MILLER LARRY C ET AL) 16 June 1992 (1992-06-16) example 2 ---	1,24,25
X	US 3 746 490 A (MARSLAND W ET AL) 17 July 1973 (1973-07-17) example 2 ---	1,24,25
X	US 5 708 017 A (DAVE KAUSHIK J ET AL) 13 January 1998 (1998-01-13) example 4 --- -/--	1,24,25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2001	25. 05. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Borst, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/01155

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 891 211 A (WINSTON ANTHONY E) 2 January 1990 (1990-01-02) table I	1,24,25
X	US 4 605 563 A (HEINE CHRISTIAN ET AL) 12 August 1986 (1986-08-12) column 1, line 53 -column 1, line 62	1,2,4, 6-9,21, 24-27,38
P,X	WO 00 56346 A (J P M E D LTD ;FRIEDMAN DORON I (IL)) 28 September 2000 (2000-09-28) example 11	1,24,25

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/01155

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-40 and 43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition (Rule 39.1(iv) PCT).

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/01155

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0181525 A	21-05-1986	AT 80299 T	15-09-1992
		AU 586202 B	06-07-1989
		AU 4978785 A	22-05-1986
		CA 1256376 A	27-06-1989
		DE 3586620 A	15-10-1992
		DE 3586620 T	08-04-1993
		DK 521585 A	14-05-1986
		ES 548746 D	01-04-1986
		ES 8605154 A	16-08-1986
		JP 1918785 C	07-04-1995
		JP 6047538 B	22-06-1994
		JP 61122213 A	10-06-1986
		US 4781920 A	01-11-1988
		ZA 8508673 A	30-07-1986
US 5122377 A	16-06-1992	NONE	
US 3746490 A	17-07-1973	AU 471129 B	27-06-1974
		AU 5038472 A	27-06-1974
		BE 792990 A	19-06-1973
		DE 2262139 A	05-07-1973
		FR 2177709 A	09-11-1973
		GB 1372950 A	06-11-1974
		IT 998084 B	20-01-1976
US 5708017 A	13-01-1998	AU 703755 B	01-04-1999
		AU 5379796 A	23-10-1996
		BR 9604803 A	09-06-1998
		CA 2217515 A	10-10-1996
		CN 1185107 A	17-06-1998
		CZ 9703135 A	15-04-1998
		EA 87 B	25-06-1998
		EP 0819004 A	21-01-1998
		HU 9801626 A	01-02-1999
		JP 11503160 T	23-03-1999
		NO 974589 A	03-12-1997
		PL 322619 A	02-02-1998
		SK 135097 A	03-06-1998
		TR 9701117 T	21-02-1998
		WO 9631213 A	10-10-1996
		ZA 9602657 A	09-10-1996
US 4891211 A	02-01-1990	CA 1329138 A	03-05-1994
		DE 3921133 A	18-01-1990
		FR 2633514 A	05-01-1990
		GB 2220141 A,B	04-01-1990
		JP 2069609 C	10-07-1996
		JP 2243616 A	27-09-1990
		JP 7103010 B	08-11-1995
		SE 469208 B	07-06-1993
		SE 8902319 A	30-12-1989
US 4605563 A	12-08-1986	DE 3340680 A	23-05-1985
		EP 0141410 A	15-05-1985
		US 4654220 A	31-03-1987
WO 0056346 A	28-09-2000	AU 3320100 A	09-10-2000
		EP 1077713 A	28-02-2001